Cross-cultural Adaption and Validation of the Zurich Chronic Middle Ear Inventory Translated Into Italian (ZCMEI-21-It)—a Prospective Multicenter Study

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Abstract: OBJECTIVE: There are no instruments available to comprehensively assess health-related quality of life (HRQoL) in chronic otitis media (COM) in Italian-speaking countries. The Zurich chronic middle ear inventory (ZCMEI-21) is a well-established instrument for the assessment of HRQoL in COM. The objective of this study was to translate and cross-culturally adapt the ZCMEI-21 into Italian and validate this questionnaire for measuring HRQoL in patients with COM. STUDY DESIGN: Prospective multicenter study. SETTING: Three University hospitals (northern Italy, central Italy, southern Italy). PATIENTS: Adult patients suffering from COM (n = 128). INTERVENTION: Following international guidelines, the ZCMEI-21 was translated into Italian (ZCMEI-21-It). Validation was performed by psychometric test statistics. Moreover, ZCMEI-21-It total and subscale scores were compared and correlated with 1) the scores of the original validation study, 2) to a question that directly addresses HRQoL, and 3) to the scores of the EQ-5D-5L, a generic questionnaire assessing HRQoL. RESULTS: From three study centers, a total of 128 patients with COM were included. Cronbach's was 0.86 indicating a high reliability. Between the ZCMEI-21-It total score and the question that directly addresses HRQoL, we found a strong correlation ($r = 0.62$, $p < 0.0001$). Between the ZCMEI-21-It total score and the EQ-5D-5L scores, we expectedly found moderate correlations (descriptive system score: $r = 0.39$, $p < 0.0001$; visual analog scale: $r = 0.30$, $p = 0.008$). CONCLUSION: We translated the ZCMEI-21 questionnaire into Italian and validated the ZCMEI-21-It in a prospective multicenter study. The ZCMEI-21-It is the first instrument that comprehensively assesses relevant dimensions of HRQoL in Italian-speaking patients affected by COM.

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Cross-cultural Adaption and Validation of the Zurich Chronic Middle Ear Inventory Translated Into Italian (ZCMEI-21-It)—a Prospective Multicenter Study

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Objective: There are no instruments available to comprehensively assess health-related quality of life (HRQoL) in chronic otitis media (COM) in Italian-speaking countries. The Zurich chronic middle ear inventory (ZCMEI-21) is a well-established instrument for the assessment of HRQoL in COM. The objective of this study was to translate and cross-culturally adapt the ZCMEI-21 into Italian and validate this questionnaire for measuring HRQoL in patients with COM.
Study Design: Prospective multicenter study.
Setting: Three University hospitals (northern Italy, central Italy, southern Italy).
Patients: Adult patients suffering from COM ($n = 128$).
Intervention: Following international guidelines, the ZCMEI-21 was translated into Italian (ZCMEI-21-It). Validation was performed by psychometric test statistics. Moreover, ZCMEI-21-It total and subscale scores were compared and correlated with 1) the scores of the original validation study, 2) to a question that directly addresses HRQoL, and 3) to the scores of the EQ-5D-5L, a generic questionnaire assessing HRQoL.
Results: From three study centers, a total of 128 patients with COM were included. Cronbach's α was 0.86 indicating a high reliability. Between the ZCMEI-21-It total score and the question that directly addresses HRQoL, we found a strong correlation ($r = 0.62$, $p < 0.0001$). Between the ZCMEI-21-It total score and the EQ-5D-5L scores, we expectedly found moderate correlations (descriptive system score: $r = 0.39$, $p < 0.0001$; visual analog scale: $r = 0.30$, $p = 0.008$).
Conclusion: We translated the ZCMEI-21 questionnaire into Italian and validated the ZCMEI-21-It in a prospective multicenter study. The ZCMEI-21-It is the first instrument that comprehensively assesses relevant dimensions of HRQoL in Italian-speaking patients affected by COM.
Key Words: Cholesteatoma patient-reported outcome measure—Chronic otitis media—Health-related quality of life—Italian—ZCMEI-21.

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Chronic (suppurative) otitis media (COM) is a chronic inflammation of the middle ear and mastoid mucosa characterized by a tympanic perforation lasting > 6 to 12 weeks which usually leads to a persistent or recurrent discharge from the middle ear (1). Chronic otitis media is a leading cause of health care visits, antibiotic prescriptions, and surgery (2,3); it causes preventable conductive hearing loss and increases the risk for permanent sensorineural hearing loss (4–6). The global incidence rate of COM is estimated at 4.8 new episodes per 1,000 people, with a total annual number of cases of 31 million (35). A World Health Organization report suggests that 65 to 350 million individuals are suffering from COM globally (7).

In the assessment of COM and its treatment, patient-reported outcomes (PROs) are gaining increasing importance and are often used in addition to objective outcome measures, such as audiometric results (8). In contrast to objective outcomes, PROs represent a subjective assessment of the patient's perspective, which may not be reflected by objective outcomes. One of the most important PROs is health-related quality of life (HRQoL) (9), which is assessed by patient-reported outcomes measures (PROMs), usually in the form of questionnaires completed by the patient. Comparing PROM scores before and after an intervention can be used in the outcome analysis of an intervention, to evaluate its possible effectiveness (10). As

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specific symptoms and their consequences impair HRQoL in COM, generic questionnaires generally are not well suited for COM due to their lack of sensitivity to reliably detect relevant aspects of HRQoL (6,11,12). Nonetheless, several generic questionnaires, especially questionnaires including a hearing loss domain, have been applied to specific otologic conditions, e.g., the Hearing Handicap Inventory or the Health Utilities Index Mark 3 (13,14).

There have been several attempts to assess QoL in adult COM. To date, five questionnaires have been developed to assess relevant symptoms and dimensions of HRQoL in COM: the Chronic Ear Survey (CES; available in English, Chinese, Korean, and Italian) (15), the English Chronic Otitis Media 5 (COM-5) (16), the German Chronic Otitis Media Outcome Test 15 (COMOT-15) (17), the Chronic Otitis Media Questionnaire 12 (COMQ-12; available in English, Dutch, and Russian) (18) and the Zurich Chronic Middle Ear Inventory 21 (ZCMEI-21; available in German and Japanese) (19).

To provide a comparable and consistent assessment of HRQoL in different countries, questionnaires should be available in multiple languages. Only one of five available questionnaires for COM was developed and validated in the Italian-speaking countries, the CES-I questionnaire (20). The CES-I appears to be a reliable and valid instrument for the investigation of health status among Italian-speaking patients with COM. However, the CES has several shortcomings as it does not include vertigo/balance problems and tinnitus. Moreover, there is no comprehensive assessment of psychosocial problems as there is only one question, which is exclusively focused on restrictions due to hearing impairment. Similar shortcomings have also been pointed out for the COMOT-15 and the COMQ-12 previously (19): the COMOT-15 is strongly focused on restriction of activities due to hearing impairment while the impact of other symptoms is not evaluated. The COMQ-12 does not assess activity restriction due to COM, which is also part of the CES, and does not provide a comprehensive assessment of psychosocial problems.

The ZCMEI-21 is a German-language questionnaire published in 2016, which provides a comprehensive assessment of HRQoL in COM patients, especially concerning psychological and social aspects (19). The ZCMEI-21 questionnaire consists of 21 items grouped into four subscales: 1) ear signs and symptoms; 2) hearing; 3) psychosocial impact; and 4) medical resources. Answers are presented using a 5-point Likert scale that ranges from 0 (no emotional or physical impact) to 4 (severe emotional or physical impact). The ZCMEI-21 has been recently validated in the Japanese language (21) and is currently being translated in other languages.

The aim of this multicenter study was to translate and cross-culturally adapt the ZCMEI-21 into Italian and validate this new Italian-language questionnaire for measuring HRQoL in patients with COM.

METHODS

This multicenter study included patients recruited in three large Italian university hospitals. The involved centers were the Sapienza University of Rome, Policlinico Umberto I (central Italy), the University of Turin, Ospedale Molinette (northern Italy), and the Aldo Moro University of Bari (southern Italy). The inclusion criteria were the diagnosis of COM with or without cholesteatoma, age $\geq$ 18 years and sufficient Italian language skills. Further details on the study design are provided in Figure 1. The study was approved by the local Ethics Committees and was performed in accordance with the Helsinki declaration and its amendments. Informed consent was obtained from all the participants.

Translation of the ZCMEI-21 Into Italian and Cross-cultural Adaptation

The translation and cross-cultural adaptation of ZCMEI-21 was performed following the Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes Measures according to the International Society for Pharmacoeconomics and Outcomes Research Task Force (22).

First, two forward translations were performed by two translation agencies specialized in medical translations. Then, the two translations were merged into a single translation by Italian speaking clinicians (ZCMEI-21-It, v1). This version of ZCMEI-21-It was reviewed by the involved physicians and was used for a first pilot test (cognitive debriefing 1) in five patients to detect difficulties in understanding of the questions and identify items that may not be well suited. The feedback received by the patients and the clinicians led to several minor modifications of the initial version. No items were excluded. The modified questionnaire constituted the second version of the ZCMEI-21-It (ZCMEI-21-It, v2). Last, a third translation agency specialized in medical translations carried out a back translation of the ZCMEI-21-It, v2, into German. After reviewing the back translation against the original German version, the ZCMEI-21-It underwent some further minor modifications to provide a conceptually equivalent Italian translation (ZCMEI-21-It, v3). Using the latter version, a second cognitive debriefing was performed leading to no additional modifications. At the end of the translation process, the final version of the questionnaire (ZCMEI-21-It) was obtained and used for the validation process (see Supplemental Digital Content 1, http://links.lww.com/MAO/A730).

Validation Process

The ZMCEI-21-It and the EuroQol five-dimensional questionnaire (EQ-5D) in its five-level version (EQ-5D-5L) were administered to COM patients meeting the inclusion criteria during ambulatory visits.

The EQ-5D-5L is a quickly administered and internationally recognized instrument aimed to obtain a meaningful description and measurement of health-related quality of life. The EQ-5D-5L questionnaire is composed of five questions that are converted to an index value (EQ-5D-5L descriptive system score; it ranges from 0 to 1, where 1 corresponds to a perfect QoL) and a visual analogue scale (EQ-5D-5L visual analog scale (VAS), that ranges from 0 to 100, where 100 corresponds to the best health state). The five questions in the EQ-5D-5L questionnaire investigate mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D-5L questionnaire has been validated in the Italian language (23); however, no specific value set has been developed for Italian. As a replacement, the UK or the Spanish sets are conventionally used to conduct evaluations in the Italian population (24–26). In the present study, a value set for England was used (27).

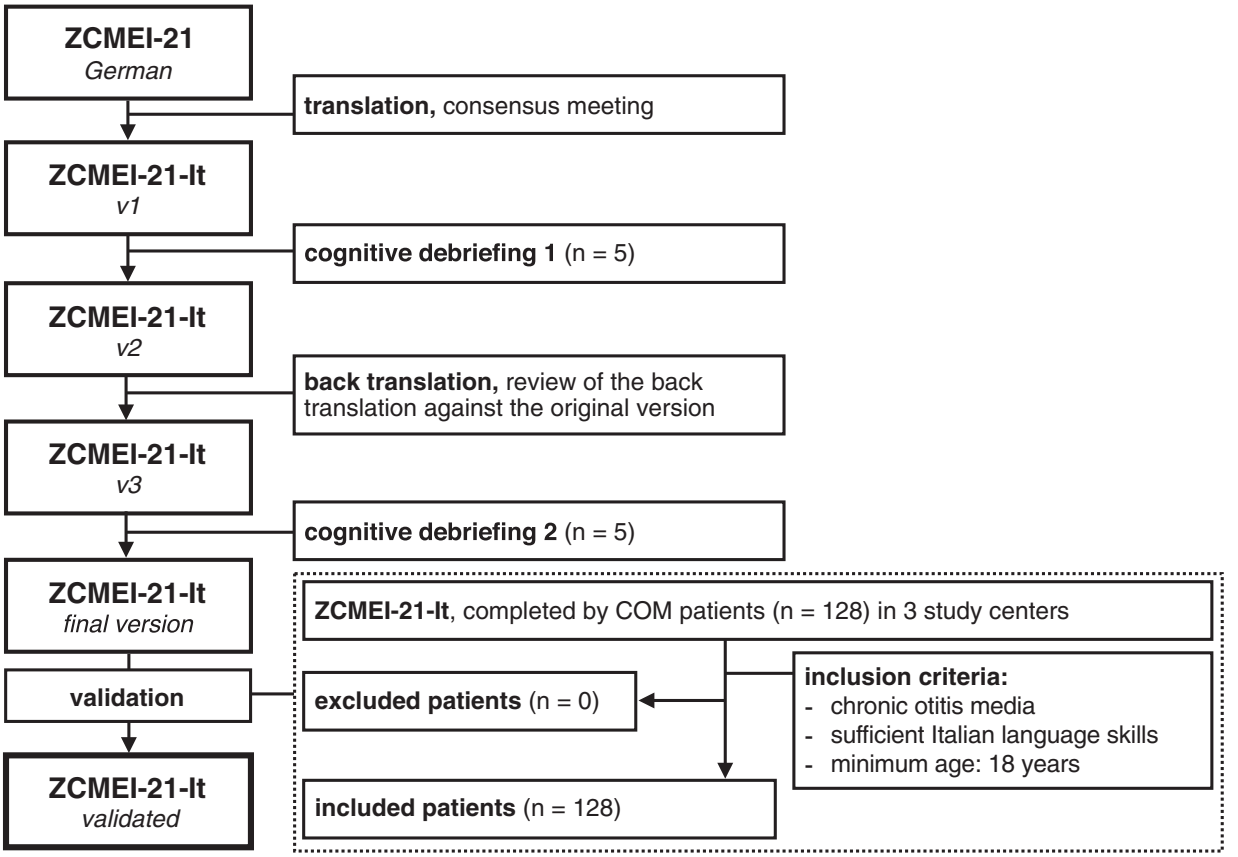

FIG. 1. Study design for the translation of the ZCMEI-21 into the Italian language questionnaire (ZCMEI-21-It) and validation of the ZCMEI-21-It. ZCMEI-21 indicates zurich chronic middle ear inventory.

As done in the original validation study (19), a general question was added to directly address HRQoL (question 22, ''My ear illness is worsening my quality of life.... not at all/ mildly/ moderately/severely/very severely'') for assessment of the criterion validity.

The minimal sample size considered for this study was 84 patients, based on a subject to item ratio of 4:1 (21 items) (28).

Statistical Analysis

All statistical tests were selected before data collection. Values are reported as mean ± SD or as absolute number and percentage. Item total-correlation was calculated to assess if an item correlates with the total score. Internal consistency as an indicator of reliability was determined by calculation of Cronbach's α. Frequency distribution was analyzed by inspection of the histogram and statistical normality tests (D'Agostino and Pearson normality test, Shapiro–Wilk normality test; for both tests, $p > 0.05$ indicates normal distribution). Criterion validity was assessed using an additional general question (question 22) that directly addressed HRQoL. Concurrent validity was determined by comparing total scores of ZCMEI-21-It and subscores to the EQ-5D-5L descriptive system and VAS scores using Spearman rank correlation and linear regression analysis including mean prediction intervals. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, NY) and Prism (version 7 for Apple Macintosh, GraphPad Software). The significance level was set to $p < 0.05$.

RESULTS

One hundred twenty-eight patients were enrolled in the study and completed the ZCMEI-21-It and the EQ-5D-5L questionnaires in the three centers involved in this multicenter study: Sapienza University of Rome, Policlinico Umberto I (48 patients), the University of Turin, Ospedale Molinette (39 patients), and the Aldo Moro University of Bari (41 patients). Mean age was 54.1 ± 19.0 years. Chronic otitis media without cholesteatoma was found in 79 patients (61.7%); cholesteatoma was present in 49 (38.3%) patients. Chronic otitis media was unilateral in 105 patients (82%) and bilateral in 23 patients (18%). Detailed demographics and clinical characteristics are shown in Table 1. For all the items, we found well distributed answers with the full range of answers used in every question as well as item means close to two, i.e., the middle value of possible answers (Table 2). Item-total-correlation of the single items was assessed as an indicator whether an item correlates well with the total score. An item-total-correlation of ≥ 0.3 is regarded as a good correlation with the total score thus being a criterion for an important item. Of the ZMCEI-21-It, only three items had an item-total-correlation of < 0.3 (Table 2). Yet, all of these items were regarded as integral part of the questionnaire and moreover, the

TABLE 1. *Demographics and clinical characteristics of the patients*

	Validation Cohort (n = 128)
Males—no. (%)	69 (53.9%)
Females—no. (%)	59 (46.1%)
Age (± SD)	54.1 ± 19.0 yr
COM, type—no. (%)	
COM without cholesteatoma	79 (61.7%)
COM with cholesteatoma	49 (38.3%)
Affected ear (s)—no. (%)	
Right	48 (37.5%)
Left	57 (44.5%)
Bilateral	23 (18.0%)
Previous surgery for COM—no. (%)	
Had previous surgery	54 (42.2%)
No previous surgery	74 (57.8%)

COM indicates chronic otitis media.

TABLE 2. *Single item descriptive statistics of the ZCMEI-21-It*

	Mean	Min–Max	ITC
Ear signs and symptoms			
Ear pain	1.05	0–4	0.50
Discharge	1.26	0–4	0.43
Itching	1.06	0–4	0.49
Feeling of pressure	1.24	0–4	0.59
Balance	0.91	0–4	0.50
Hearing			
Tinnitus	1.65	0–4	0.50
Hearing (filter question)	1.66	0–4	0.14
When many people speak at the same time	1.37	0–4	0.21
Telephone, alarm-clock	1.49	0–4	0.17
Fear of not hearing other people	1.40	0–4	0.36
Psychosocial impact			
Impact of ear symptoms on HRQoL	2.11	0–4	0.53
Protection from water	1.45	0–4	0.47
Activities with family and friends	1.49	0–4	0.57
In public (e.g., occupation, shopping)	1.55	0–4	0.51
Making contact with other people	1.07	0–4	0.56
Quality of sleep	1.65	0–4	0.63
Sadness	2.47	0–4	0.41
Fear that the ear problems may persist	1.96	0–4	0.32
Medical resources			
Medical consultations	1.18	0–4	0.45
Antibiotics (oral)	0.84	0–4	0.46
Ear drops	0.93	0–4	0.50

ITC item-total-correlation, min lowest value, max highest value; answers to the ZCMEI-21-It are presented using a five-point scale ranging from 0 (no emotional or physical impact) to 4 (severe emotional or physical impact).

ZCMEI-21 indicates zurich chronic middle ear inventory.

present study was not set up for an item reduction process. Therefore, no items were excluded because of statistical criteria. Internal consistency was determined as a measure of the questionnaire's reliability. We found a Cronbach's α of 0.86, which indicates a high internal consistency. Distribution of the answers showed a normal (Gaussian) distributed as evidenced by inspection of the histogram (Fig. 2A) and normality tests (D'Agostino and Pearson normality test, $p = 0.12$; Shapiro–Wilk normality test, $p = 0.22$). Next, we assessed total scores in subgroups of the study population to identify any confounders affecting the ZCMEI-21-It total score and the subsequent subscale analysis. We found no significant differences in the mean total scores neither when patients were grouped according to having had surgery before nor according to the COM subtype (Fig. 2, B and C).

Next, we compared ZCMEI-21 total and subscale scores as well as their correlation with the EQ-5D-5L descriptive system score between the original validation study (19) and our translated version, the ZCMEI-21-It. This comparison showed highly similar values for total scores, subscale scores, and correlation coefficients (Table 3). The only exception was correlation of the ZCMEI-21-It total score and the EQ-5D-5L descriptive system score. The ZCMEI-21-It total score showed a strong correlation with the question that directly assesses HRQoL (question #22; $r = 0.62$, $p < 0.0001$; Fig. 3A), indicating a high criterion validity. In contrast, there was only a low to moderate correlation between the ZCMEI-21-It total score and the EQ-5D-5L descriptive system score ($r = 0.39$, $p < 0.0001$) and the EQ-5D-5L VAS ($r = 0.30$, $p = 0.008$). Moreover, the ZCMEI-21-It subscale scores were correlated to the EQ-5D-5L descriptive system and VAS scores. The subscale score for ''ear signs and symptoms'' was weakly to moderately correlated to the EQ-5D-5L scores (Fig. 4, A and B; to EQ-5D-5L descriptive system score: $r = 0.43$, $p < 0.0001$; to EQ-5D-5L VAS: $r = 0.21$, $p = 0.02$). No significant correlation was found between the subscale score for ''hearing'' and the EQ-5D-5L scores (Fig. 4, C and D; to EQ-5D-5L descriptive system score: $p = 0.62$; to EQ-5D-5L VAS: $r = 0.57$). Last, a significant but moderate correlation was found between the subscale score for ''psychosocial impact'' and the EQ-5D-5L scores (Fig. 4, C and D; to EQ-5D-5L descriptive system score: $r = 0.27$, $p = 0.002$; to EQ-5D-5L VAS: $r = 0.25$, $p = 0.004$).

DISCUSSION

Here, we translated the ZCMEI-21 questionnaire into the Italian language, i.e., the ZCMEI-21-It, and validated the ZCMEI-21-It in a prospective multicenter study. The ZCMEI-21-It is the first Italian instrument that comprehensively assesses relevant symptoms and dimensions of HRQoL in Italian-speaking patients affected by COM.

In current clinical practice, HRQoL in patients with COM in Italian-speaking countries is measured using a generic questionnaire called the Short Form 36 Health Survey, validated in the Italian language in 1998 (29).

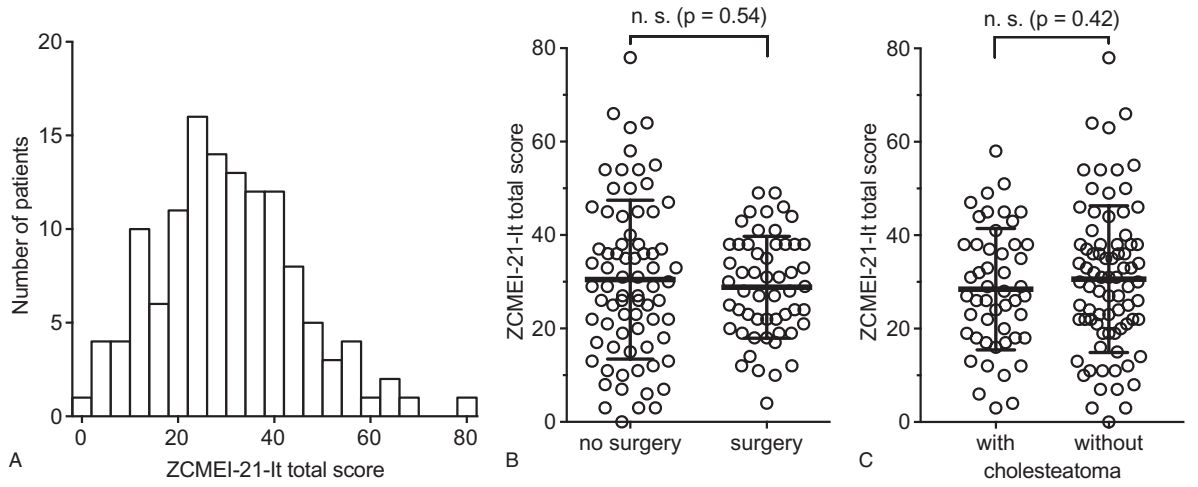

FIG. 2. *A*, Frequency distribution of the ZCMEI-21-It (bin width on *x* axis: 4). *B*, *C*, Comparison of ZCMEI-21-It total scores between preoperative and postoperative patients with COM *(B)* and between patients suffering from COM with and without cholesteatoma *(C)*. Unpaired *t* test, whiskers indicates standard deviation range, bold horizontal line represents mean. COM indicates chronic otitis media; ZCMEI-21, zurich chronic middle ear inventory.

TABLE 3. *Total score and subscale scores of the ZCMEI-21-It and its correlation to the EQ-5D-5L*

	Current Study, ZCMEI-21-It (n = 128)	Original Validation Study, ZCMEI-21 (n = 76)
ZCMEI-21-It/ZCMEI-21 total score (± SD)	29.8 ± 14.6	29.7 ± 16.1
Ear signs and symptoms	5.5 ± 4.5	5.1 ± 3.9
Hearing	7.6 ± 5.1	8.5 ± 5.2
Psychosocial impact	13.7 ± 7.8	13.1 ± 7.9
Medical resources	2.9 ± 2.7	3.0 ± 2.3
EQ-5D-5L (± SD)		
Descriptive system score	0.84 ± 0.15	0.92 ± 0.14
VAS score	76.6 ± 15.0	NA
Total score correlation (a)		
To question directly assessing HRQoL	r = 0.62, $p < 0.0001$	r = 0.74, $p < 0.0001$
To EQ-5D-5L descriptive system score	r = 0.39, $p < 0.0001$	r = 0.60, $p < 0.0001$

Spearman's rank correlation coefficient, *p* value.

ZCMEI-21 indicates zurich chronic middle ear inventory; EQ-5D-5L, EuroQol five-dimensional questionnaire in its five-level version; VAS, visual analog scale.

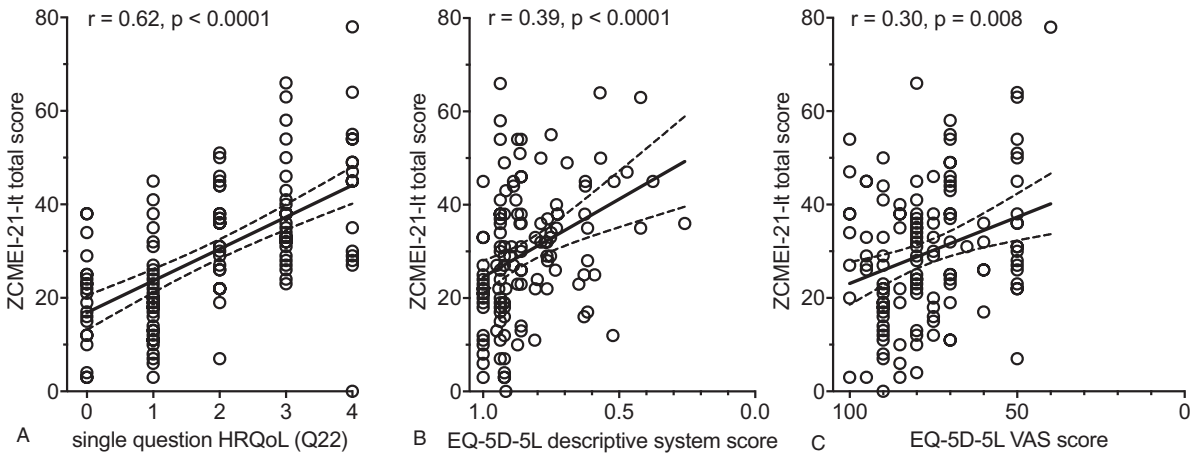

FIG. 3. *A*, Correlation for ZCMEI-21-It total scores and the question #22, which directly assessed HRQoL (0 on the *x* axis: no impact on HRQoL in question #22; 4 on the *x* axis: huge impact on HRQoL in question #22; Spearman rank correlation). *B, C*, Correlation between ZCMEI-21-It total score and EQ-5D-5L descriptive systems score *(B)* as well as the EQ-5D-5L VAS *(C)*. Solid line indicates linear regression line, dashed lines indicates 95% prediction interval, r, Spearman's rank correlation coefficient. ZCMEI-21 indicates zurich chronic middle ear inventory; HRQoL, health-related quality of life; EQ-5D-5L, EuroQol five-dimensional questionnaire in its five-level version; VAS, visual analog scale.

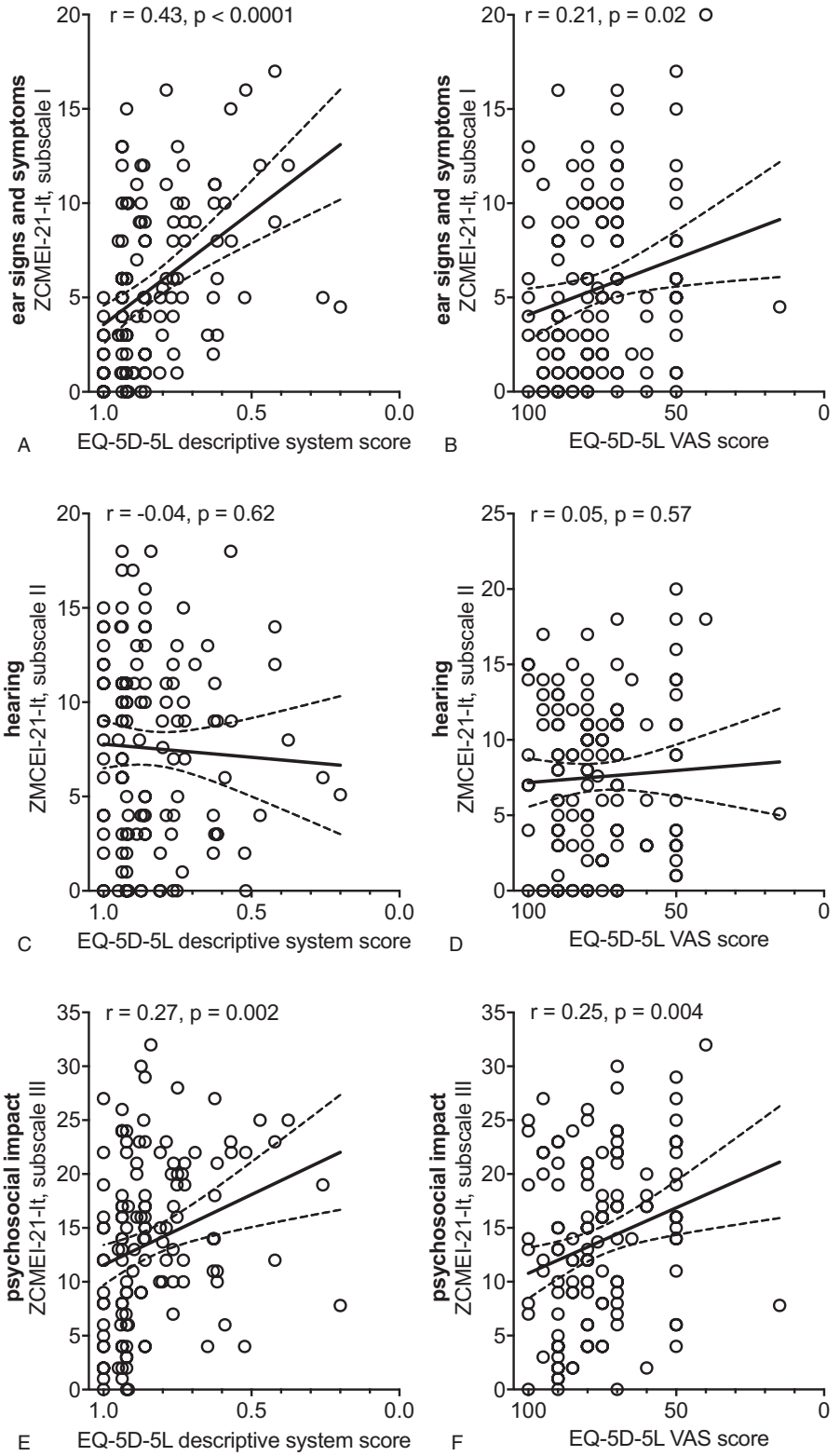

FIG. 4. Spearman rank correlation between ZCMEI-21-It subscale scores and EQ-5D-5L scores (descriptive system score and VAS). Solid line represents linear regression line, dashed lines represent 95% prediction interval, r, Spearman's rank correlation coefficient. ZCMEI-21 indicates zurich chronic middle ear inventory; EQ-5D-5L, EuroQol five-dimensional questionnaire in its five-level version; VAS, visual analog scale.

However, Short Form 36 Health Survey has proven not to be sensitive enough for the COM condition (15). To compensate for this lack, a more specific questionnaire for COM, the CES questionnaire, has been recently translated and validated in Italian (CES-I) (20). The CES-I proved to be a valid, disease-specific health measure that can be used to evaluate adult patients with COM among the Italian-speaking population (20). However, the CES-I primarily focuses on disease-specific health and lacks specific assessment of the impact of single symptoms on the QoL. Although the ZCMEI-21 is partially based on the CES questionnaire, it differs in several relevant aspects and has multiple advantages as it has been developed to overcome the above limitations of the CES and other questionnaires (19). Therefore, the use of the ZCMEI-21 questionnaire in Italian language patients may be a useful tool to be applied and may also be used in conjunction with the CES-I questionnaire.

The translation of the ZCMEI-21 questionnaire in the Italian language followed a standardized approach involving both patients and clinicians. In the validation process, we assessed the reliability and validity of the ZCMEI-21-It. We found an excellent Cronbach's α, which provides evidence of the questionnaire's reliability. As expected, only moderate correlation between the EQ-5D-5L and the ZCMEI-21-It total score was found. In particular, weak to moderate correlations were found for the ear signs and symptoms subscale as well as the psychosocial impact subscale. This data provide evidence that the ZCMEI-21-It in fact measures the complex construct of HRQoL; yet it also underscores the fact that generic questionnaires generally are less reliable in assessing HRQoL in specific conditions. The EQ-5D-5L constitutes a generic HRQoL questionnaire and does therefore not meet the requirements of assessing detailed HRQoL in specific diseases, such as COM (30). Interestingly, no correlation could be found between the ZCMEI-21-It subscale score of ''hearing'' and the EQ-5D-5L, meaning that the patient's subjective hearing ability does not well correlate to the perceived HRQoL in COM. Similar findings have also been demonstrated in other studies (30,31). This may further corroborate the application of specific PROMs in COM which do not only account for hearing impairment as the sole factor affecting HRQoL.

The cohort included in the present validation study included both patients that already underwent surgery for COM and patients that did not undergo surgery. Furthermore, both types of COM, i.e., COM with and without cholesteatoma, were included. This is similar to the cohort of the original ZCMEI-21 study, as the questionnaire has been developed to evaluate both pre- and postoperative HRQoL in patients with both COM with and without cholesteatoma. Thus, the ZCMEI-21 and its translations are suited for research purposes as well as for application in the clinical routine for the entire spectrum of COM and both pre- and postoperatively.

In the present study, an article-based version of the ZCMEI-21-It has been used. In contrast, the original ZCMEI-21 was developed as an electronic questionnaire delivered on a tablet computer. Yet, similar results are expected in article-based and electronic application of questionnaires (32). Therefore, the use of both article-based and electronic versions of the ZCMEI-21-It is justified based on the present validation data.

CONCLUSION

In the present article, we undertook an Italian translation of the ZCMEI-21 questionnaire according to standardized guidelines. In the subsequent validation study, we acquired ample evidence demonstrating that the ZCMEI-21-It is a reliable and valid questionnaire. Hence, this new Italian-language questionnaire can be used to quantify HRQoL in COM in both patients with and without cholesteatoma, and regardless of whether they had undergone surgery for COM.

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